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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/615,854	07/14/2000	Keith L. Black	CEDAR-044569	4523

7590 07/28/2004

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/615,854	BLACK ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *303-320* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence compliance documents*.

Continuation of Disposition of Claims: Claims pending in the application are 1-3,12,13,18-24,48,57-60,65-71,135-137,151-153,195-234,240-272,278-284 and 287-320.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 1-3,12,13,18-24,48,57-60,65-71,135-137,151-153,195-234,240-272,278-284 and 287-302.

DETAILED ACTION

Claims 1-3, 12, 13, 18-24, 48, 57-60, 65-71, 135-137, 151-153, 195-234, 240-272, 278-284 and 287-320 are currently pending in the application. Claims 1-3, 12, 13, 18-24, 48, 57-60, 65-71, 135-137, 151-153, 195-234, 240-272, 278-284 and 287-302 are withdrawn from consideration. Claims 303-320 are currently under examination.

This Office Action is in response to the amendment filed on 6/4/04.

Response to Amendment

Newly submitted/amended claims 1-3, 12, 13, 18-24, 48, 57-60, 65-71, 135-137, 151-153, 195-234, 240-272, 278-284 and 287-302 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: These claims are drawn to a method of delivering a medicant to an abnormal brain region or a malignant tumor in a mammalian subject by administering a direct agonist of calcium activated potassium channel to increase the permeability to the medicant to said region, a pharmaceutical composition and a kit comprising the direct agonist of calcium activated potassium channel. The originally elected claims are drawn to a method of delivering a medicant to an abnormal brain region or a malignant tumor in a mammalian subject by administering an *in vivo* activator of calcium activated potassium channel to said mammal, wherein said activator is an activator of soluble guanylyl cyclase, and a pharmaceutical composition and a kit comprising said activator of soluble guanylyl cyclase. Thus, the current pending claims are drawn to a different invention than what is elected originally.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for

prosecution on the merits. Accordingly, claims 1-3, 12, 13, 18-24, 48, 57-60, 65-71, 135-137, 151-153, 195-234, 240-272, 278-284 and 287-302 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Newly added claims 303-320 stand rejected under 35 U.S.C. 112 1st paragraph for reasons set forth of the record mailed on 1/15/03 and further discussed below.

Newly added claims 306, 309-312, 316, 317, 319 and 320 are rejected under 35 U.S.C. 112, 2nd paragraph for reasons set forth below.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132. (see attached error report)

Applicants are reminded that failure to comply with the requirements will result in abandonment of the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 303-313 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering a medicant having a molecular weight between 50 Daltons and about 250 KD or a particle diameter between about 50 to 250 nanometers to a glioma, ischemia or stroke region in the brain of a mammalian subject by administering an effective amount of YC1 by intracarotid infusion simultaneously with the medicant, does not reasonably provide enablement for a method of delivering any medicant to any kind of abnormal brain region by administering Ca dependent potassium channel activator of the guanylyl cyclase activator by any route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Claims 303-313 are rejected for same reasons as applied to original claims 1-10, 12-24, 48-55, 57-71, 135-144, 146-160 and 162-189 as discussed in the Office Action mailed on 1/15/03. In response to the rejection, Applicants have provided a publication by Ningaraj et al., and assert that the data presented by the reference establishes that the claimed method permits enhanced delivery of medicants to a broad range of abnormal brain regions or tumors and a variety mode of administration. Applicants argue that this reference demonstrated that medicant of large size, such as 371KD, and vectors can be delivered to abnormal brain region. Applicants further argue that the Declaration filed on 1/23/04 by Dr. Ningaraj further established enhanced uptake of compounds in brain tumors other than glioma, which includes metastatic breast brain tumors and metastatic brain tumors. Furthermore, the Declaration assert that metastasized brain cancer cells originating from lung, breast and renal cancer cells all have high levels of K_{ATP} channel

expression on both the cancerous cells and on capillary endothelium. Moreover, Applicants argue that the Declaration has demonstrated that the delivery of the compound is not limited to intra-carotid infusion.

These arguments has been fully considered but deemed unpersuasive. The cited reference teaches a method of delivering medicants through K_{ATP} channel activator, rather than YC1, an activator of calcium activated potassium channel. The experimental data provided by the Ningaraj declaration addresses the method of delivering medicant to abnormal brain region using K_{ATP} channel activator. As such, both the reference and the Declaration relied upon by Applicants to support the enablement of the instant invention fails to provide such support because of the difference of the subject matter. As such, without evidence from the contrary, the claimed invention is enabled to the scope of a method of delivering a medicant having a molecular weight between 50 Daltons and about 250 KD or a particle diameter between about 50 to 250 nanometers to a glioma, ischemia or stroke region in the brain of a mammalian subject by administering an effective amount of YC1 by intracarotid infusion simultaneously with the medicant. Therefore, this rejection is maintained.

Claims 314-320 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is a pharmaceutical composition comprising a combination of YC-1, formulated in a pharmaceutically acceptable solution together with a medicant of different nature and chemical property.

The breadth of the claims is very broad, since the claims encompass any type of medicant ranging from chemical compounds, diagnostics, nucleic acid molecules and proteins. The 112 1st paragraph statue requires the specification not only have to support how to make of the claimed invention, but also how to use the claimed invention. The teaching of the specification is limited with regard how to use the claimed invention as a pharmaceutical composition. The specification does not teach what types of disease these compositions can treat, and whether a therapeutic effect is achieved. As such, whether the claimed pharmaceutical compositions have any therapeutic effect is unpredictable.

The state of art is silent with regard to a pharmaceutical composition comprising YC-1 and other medicants. Without such teaching, one of skilled in the art would have to rely on the guidance provided in the specification to use the claimed invention as a pharmaceutical composition. However, the specification does not provide such guidance or working examples for how to use the claimed invention as pharmaceutical compositions. As such, one skilled in the art would have to engage in undue experimentation to use the invention as claimed. Therefore, the claimed invention is not enabled by the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 306, 309-312, 316, 317, 319 and 320 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 306, the recitation of "a region a tissue" renders the claim indefinite because it is unclear whether it is referring to a region and a tissue, or a region or a tissue. Clarification is required.

Regarding claims 309, it appears that there are two claims with number 309. Appropriate re-numbering is required.

Regarding claims 309, 310, 316 and 317, the recitation of "wherein the therapeutic cytotoxic agent is cisplatin, carboplatin..." and "wherein the anticancer chemotherapeutic agent is daunrubicin, doxorubicin" renders the claims indefinite because all the recited drugs appear to be anticancer chemotherapeutic agent. It is thus unclear what is the difference between the therapeutic cytotoxic agent and the anticancer chemotherapeutic agent.

Regarding claim 311 and 319, the term "cytokine agonist" and "cytokine antagonist" render the claim indefinite because it is unclear what composition applicants are referring to. Agonist and antagonist are generally known to associate with receptor rather than any cytokine. The specification does not define any such cytokine agonist and antagonist. As such, it is unclear what are the metes and bounds of these terms encompass.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the

resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 312 and 320 recite the broad recitation DNA expression vector, and the claim also recites viral vector, which is the narrower statement of the range/limitation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.

Notice to Comply	Application No.	Applicant(s)	
	09/615854	Black et al.	
	Examiner	Art Unit	
	Celine Qian	1636	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒7. Other: CRF is flawed.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

Raw Sequence Listing Error Summary

ERROR DETECTED | SUGGESTED CORRECTION | SERIAL NUMBER: 09/615,854

ATTN: NEW RULES CASES: PLEASE DISREGARD ENGLISH "ALPHA" HEADERS, WHICH WERE INSERTED BY PTO SOFTWARE

1	Wrapped Nucleics Wrapped Aminos	The number/text at the end of each line "wrapped" down to the next line. This may occur if your file was retrieved in a word processor after creating it. Please adjust your right margin to .3; this will prevent "wrapping."
2	Invalid Line Length	The rules require that a line not exceed 72 characters in length. This includes white spaces.
3	Misaligned Amino Numbering	The numbering under each 5th amino acid is misaligned. Do not use tab codes between numbers; use space characters, instead.
4	Non-ASCII	The submitted file was not saved in ASCII(DOS) text, as required by the Sequence Rules. Please ensure your subsequent submission is saved in ASCII text.
5	Variable Length	Sequence(s)____contain n's or Xaa's representing more than one residue. Per Sequence Rules, each n or Xaa can only represent a single residue. Please present the maximum number of each residue having variable length and indicate in the <220>-<223> section that some may be missing.
6	PatentIn 2.0 "bug"	A "bug" in PatentIn version 2.0 has caused the <220>-<223> section to be missing from amino acid sequences(s) _____. Normally, PatentIn would automatically generate this section from the previously coded nucleic acid sequence. Please manually copy the relevant <220>-<223> section to the subsequent amino acid sequence. This applies to the mandatory <220>-<223> sections for Artificial or Unknown sequences.
7	Skipped Sequences (OLD RULES)	Sequence(s) _____ missing. If intentional, please insert the following lines for each skipped sequence: (2) INFORMATION FOR SEQ ID NO:X: (insert SEQ ID NO where "X" is shown) (i) SEQUENCE CHARACTERISTICS: (Do not insert any subheadings under this heading) (xi) SEQUENCE DESCRIPTION:SEQ ID NO:X: (insert SEQ ID NO where "X" is shown) This sequence is intentionally skipped Please also adjust the "(ii) NUMBER OF SEQUENCES:" response to include the skipped sequences.
8	Skipped Sequences (NEW RULES)	Sequence(s) _____ missing. If intentional, please insert the following lines for each skipped sequence. <210> sequence id number <400> sequence id number 000
9	Use of n's or Xaa's (NEW RULES)	Use of n's and/or Xaa's have been detected in the Sequence Listing. Per 1.823 of Sequence Rules, use of <220>-<223> is MANDATORY if n's or Xaa's are present. In <220> to <223> section, please explain location of n or Xaa, and which residue n or Xaa represents.
10	Invalid <213> Response	Per 1.823 of Sequence Rules, the only valid <213> responses are: Unknown, Artificial Sequence, or scientific name (Genus/species). <220>-<223> section is required when <213> response is Unknown or is Artificial Sequence
11	Use of <220>	Sequence(s) _____ missing the <220> "Feature" and associated numeric identifiers and responses. Use of <220> to <223> is MANDATORY if <213> "Organism" response is "Artificial Sequence" or "Unknown." Please explain source of genetic material in <220> to <223> section. (See "Federal Register," 06/01/1998, Vol. 63, No. 104, pp. 29631-32) (Sec. 1.823 of Sequence Rules)
12	PatentIn 2.0 "bug"	Please do not use "Copy to Disk" function of PatentIn version 2.0. This causes a corrupted file, resulting in missing mandatory numeric identifiers and responses (as indicated on raw sequence listing). Instead, please use "File Manager" or any other manual means to copy file to floppy disk.
13	Misuse of n	n can only be used to represent a single nucleotide in a nucleic acid sequence. N is not used to represent any value not specifically a nucleotide.